CLAIMS

What is claimed is:

1. A method of generating a differentiated human cell of a selected type, the method comprising maintaining an isolated human KDR^+ stem cell in the presence of a differentiated mammalian cell of the selected type, whereby the stem cell differentiates to become the differentiated human cell of the selected type.

2. The method of claim 1, wherein the stem cell is maintained in contact with the differentiated mammalian cell.

3. The method of claim 1, wherein the stem cell is maintained in vitro in the presence of the differentiated mammalian cell.

4. The method of claim 1, wherein the stem cell is separated from the differentiated mammalian cell by a porous barrier.

5. The method of claim 1, wherein the stem cell is isolated from a human hematopoietic tissue using a reagent that specifically binds with KDR.

6. The method of claim 5, wherein tissue is selected from the group consisting of an embryonic tissue, a fetal tissue, and a post-natal tissue.

7. The method of claim 5, wherein the tissue is an embryonic tissue selected from the group consisting of the aorta-gonad-mesonephros region tissue, yolk sac, and embryonic liver.

8. The method of claim 5, wherein the tissue is a fetal tissue selected from the group consisting of liver, bone marrow, and peripheral blood.

9. The method of claim 5, wherein the tissue is a post-natal tissue selected from the group consisting of cord blood, bone marrow, normal peripheral blood, mobilized peripheral blood, a hepatic tissue, and a splenic tissue.

10. The method of claim 5, wherein the reagent is an antibody.

11. The method of claim 10, wherein the antibody is selected from the group consisting of KDR1 and KDR2.

12. The method of claim 1, wherein the stem cell is isolated using a conjugated vascular endothelial growth factor.

13. The method of claim 1, wherein the differentiated mammalian cell is a human cell.

14. The method of claim 1, wherein the differentiated mammalian cell is a cell of ectodermal origin.

15. The method of claim 1, wherein the differentiated mammalian cell is a cell of mesodermal origin.

16. The method of claim 1, wherein the differentiated mammalian cell is a cell of endodermal origin.

17. The method of claim 1, wherein the differentiated mammalian cell is selected from the group consisting of a skeletal muscle cell, a myocardial cell, an epithelial cell, an endothelial cell, a cartilage cell, a retinal cell, a lens cell, a bone cell, a fat cell, a peripheral nerve cell, a differentiated hematopoietic cell, a marrow stromal cell, a hepatocyte, a splenocyte, a keratinocyte, a fibroblast, a lymphoid cell, and a central nervous system cell.

18. A method of repairing a damaged human tissue, the method comprising

i) maintaining an isolated human KDR^+ stem cell in the presence of a differentiated mammalian cell of a tissue of the same type as the damaged tissue, whereby the stem cell differentiates to become an altered cell selected from the group consisting of a tissue-exposed stem cell, a precursor of a cell of the same type as the damaged tissue, and a terminally differentiated cell of the same type as the damaged tissue; and

ii) providing the altered cell to the damaged tissue, thereby repairing the tissue.

19. The method of claim 18, wherein the stem cell is maintained in contact with the differentiated mammalian cell.

20. The method of claim 18, wherein the stem cell is separated from the differentiated mammalian cell by a porous barrier.

21. The method of claim 18, wherein the stem cell is isolated from a human hematopoietic tissue using a reagent that specifically binds with KDR.

22. The method of claim 21, wherein tissue is selected from the group consisting of an embryonic tissue, a fetal tissue, and a post-natal tissue.

23. The method of claim 21, wherein the tissue is an embryonic tissue selected from the group consisting of the aorta-gonad-mesonephros region tissue, yolk sac, and embryonic liver.

24. The method of claim 21, wherein the tissue is a fetal tissue selected from the group consisting of liver, bone marrow, and peripheral blood.

25. The method of claim 21, wherein the tissue is a post-natal tissue selected from the group consisting of cord blood, bone marrow, normal peripheral blood, mobilized peripheral blood, a hepatic tissue, and a splenic tissue.

26. The method of claim 21, wherein the reagent is an antibody.

27. The method of claim 26, wherein the antibody is selected from the group consisting of KDR1 and KDR2.

28. The method of claim 21, wherein the stem cell is isolated using a conjugated vascular endothelial growth factor.

29. The method of claim 18, wherein the stem cell is maintained in vitro in the presence of the differentiated mammalian cell.

30. The method of claim 18, wherein the differentiated mammalian cell is a human cell.

31. The method of claim 18, wherein the damaged tissue is associated with a disease or disorder selected from the group consisting of stroke, ischemia, myocardial infarction, coronary artery disease, spinal cord injury, age-related tissue damage, Alzheimer's disease, Parkinson's disease, liver fibrosis, liver cirrhosis, chronic obstructive pulmonary disorder, compartment syndrome, multiple sclerosis, chronic inflammation, chronic infection, macular degeneration, and cataracts.

32. A method of rejuvenating an age-damaged human tissue, the method comprising

i) maintaining an isolated human KDR^+ stem cell in the presence of a differentiated mammalian cell of a tissue of the same type as the damaged tissue, whereby the stem cell

differentiates to become an altered cell selected from the group consisting of a tissue-exposed stem cell, a precursor of a cell of the same type as the damaged tissue, and a terminally differentiated cell of the same type as the damaged tissue; and

ii) providing the altered cell to the age-damaged tissue, thereby rejuvenating the tissue.

33. The method of claim 32, wherein the stem cell is maintained in contact with the differentiated mammalian cell.

34. The method of claim 32, wherein the stem cell is separated from the differentiated mammalian cell by a porous barrier.

35. The method of claim 32, wherein the stem cell is isolated from a human hematopoietic tissue using a reagent that specifically binds with KDR.

36. The method of claim 35, wherein tissue is selected from the group consisting of an embryonic tissue, a fetal tissue, and a post-natal tissue.

37. The method of claim 35, wherein the tissue is an embryonic tissue selected from the group consisting of the aorta-gonad-mesonephros region tissue, yolk sac, and embryonic liver.

38. The method of claim 35, wherein the tissue is a fetal tissue selected from the group consisting of liver, bone marrow, and peripheral blood.

39. The method of claim 35, wherein the tissue is a post-natal tissue selected from the group consisting of cord blood, bone marrow, normal peripheral blood, mobilized peripheral blood, a hepatic tissue, and a splenic tissue.

40. The method of claim 35, wherein the reagent is an antibody.

41. The method of claim 40, wherein the antibody is selected from the group consisting of KDR1 and KDR2.

42. The method of claim 35, wherein the stem cell is isolated using a conjugated vascular endothelial growth factor.

43. The method of claim 32, wherein the stem cell is maintained in vitro in the presence of the differentiated mammalian cell.

44. The method of claim 32, wherein the differentiated mammalian cell is a human cell.

45. The method of claim 32, wherein the differentiated mammalian cell is selected from the group consisting of a skeletal muscle cell, a myocardial cell, an epithelial cell, an endothelial cell, a cartilage cell, a retinal cell, a lens cell, a bone cell, a fat cell, a peripheral nerve cell, a differentiated hematopoietic cell, a marrow stromal cell, a hepatocyte, a splenocyte, a keratinocyte, a fibroblast, a lymphoid cell, and a central nervous system cell.

46. A method of generating a differentiated human cell of a selected type, the method comprising maintaining an isolated human KDR^+ stem cell in a medium conditioned to reflect the presence of differentiated mammalian cells of the selected type in the medium, whereby the stem cell differentiates to become the differentiated human cell of the selected type.

47. The method of claim 46, wherein the medium is conditioned by culturing differentiated mammalian cells of the selected type therein.

48. The method of claim 47, wherein the differentiated cells are removed from the conditioned medium before maintaining the stem cell in the medium.

49. The method of claim 46, wherein the medium is a synthetic medium made without culturing the differentiated mammalian cells therein.

50. A method of repairing a damaged human tissue, the method comprising

i) maintaining an isolated human KDR^+ stem cell in a medium conditioned to reflect the presence of differentiated mammalian cells of the same type as the damaged tissue, whereby the stem cell differentiates to become an altered cell selected from the group consisting of a tissue-exposed stem cell, a precursor of a cell of the same type as the damaged tissue, and a terminally differentiated cell of the same type as the damaged tissue; and

ii) providing the altered cell to the damaged tissue, thereby repairing the tissue.

51. The method of claim 50, wherein the medium is conditioned by culturing differentiated mammalian cells of the selected type therein.

52. The method of claim 51, wherein the differentiated cells are removed from the conditioned medium before maintaining the stem cell in the medium.

53. The method of claim 50, wherein the medium is a synthetic medium made without culturing the differentiated mammalian cells therein.

54. A method of rejuvenating an age-damaged human tissue, the method comprising

i) maintaining an isolated human KDR^+ stem cell in a medium conditioned to reflect the presence of differentiated mammalian cells of the same type as the damaged tissue, whereby the stem cell differentiates to become an altered cell selected from the group consisting of a

tissue-exposed stem cell, a precursor of a cell of the same type as the damaged tissue, and a terminally differentiated cell of the same type as the damaged tissue; and

ii) providing the altered cell to the age-damaged tissue, thereby rejuvenating the tissue.

55. The method of claim 54, wherein the medium is conditioned by culturing differentiated mammalian cells of the selected type therein.

56. The method of claim 55, wherein the differentiated cells are removed from the conditioned medium before maintaining the stem cell in the medium.

57. The method of claim 54, wherein the medium is a synthetic medium made without culturing the differentiated mammalian cells therein.

58. An enriched population of long-term repopulating human hematopoietic stem cells obtained using a method comprising obtaining a population of cells from human hematopoietic tissue and isolating a population of KDR^+ cells therefrom, thereby obtaining a cell population enriched for long-term repopulating human hematopoietic stem cells.

59. A cell obtained using a method comprising obtaining a population of cells from human hematopoietic tissue and isolating a population of KDR^+ cells therefrom, thereby obtaining a cell population enriched for long-term repopulating human hematopoietic stem cells.

60. The cell of claim 59, wherein said cell comprises an isolated nucleic acid.

61. The cell of claim 60, wherein said isolated nucleic acid is selected from the group consisting of a nucleic acid encoding adenosine deaminase, a nucleic acid encoding beta-globin, a nucleic acid encoding multiple drug resistance, an antisense nucleic acid complementary to a human immunodeficiency virus nucleic acid, an antisense nucleic acid

complementary to a nucleic acid encoding a cell cycle gene, and an antisense nucleic acid complementary to a nucleic acid encoding an oncogene.

62. The cell of claim 60, wherein said isolated nucleic acid is operably linked to a promoter/regulatory sequence.

63. The cell of claim 62, wherein said promoter/regulatory sequence is selected from the group consisting of a retroviral long terminal repeat, and the cytomegalovirus immediate early promoter.

64. An isolated purified population of long-term repopulating human hematopoietic stem cells obtained by the method of claim 63.

65. A cell obtained by the method of claim 63.

66. The cell of claim 65, wherein said cell comprises an isolated nucleic acid.

67. The cell of claim 66, wherein said isolated nucleic acid is selected from the group consisting of a nucleic acid encoding adenosine deaminase, a nucleic acid encoding beta-globin, a nucleic acid encoding multiple drug resistance, an antisense nucleic acid complementary to a human immunodeficiency virus nucleic acid, an antisense nucleic acid complementary to a nucleic acid encoding a cell cycle gene, and an antisense nucleic acid complementary to a nucleic acid encoding an oncogene.

68. The cell of claim 66, wherein said isolated nucleic acid is operably linked to a promoter/regulatory sequence.

69. The cell of claim 68, wherein said promoter/regulatory sequence is selected from the group consisting of a retroviral long terminal repeat, and the cytomegalovirus immediate early promoter.

70. A purified population of long-term repopulating human hematopoietic stem cells obtained by a method comprising obtaining a population of cells from human hematopoietic tissue, isolating a population of hematopoietic progenitor cells therefrom, and isolating a population of KDR^+ cells from said population of hematopoietic progenitor cells, thereby obtaining a purified population of long-term repopulating human hematopoietic stem cells, wherein said hematopoietic progenitor cells are isolated by isolating $CD34^-$ using antibody which specifically binds lin to select a population of $CD34^-lin^-$ cells and using an antibody which specifically binds KDR.

71. A cell isolated by a method comprising obtaining a population of cells from human hematopoietic tissue, isolating a population of hematopoietic progenitor cells therefrom, and isolating a population of KDR^+ cells from said population of hematopoietic progenitor cells, thereby obtaining a purified population of long-term repopulating human hematopoietic stem cells, wherein said hematopoietic progenitor cells are isolated by isolating $CD34^-$ using antibody which specifically binds lin to select a population of $CD34^-lin^-$ cells and using an antibody which specifically binds KDR.

72. The cell of claim 71, wherein said cell comprises an isolated nucleic acid.

73. The cell of claim 72, wherein said isolated nucleic acid is selected from the group consisting of a nucleic acid encoding adenosine deaminase, a nucleic acid encoding beta-globin, a nucleic acid encoding multiple drug resistance, an antisense nucleic acid complementary to a human immunodeficiency virus nucleic acid, an antisense nucleic acid complementary to a nucleic acid encoding a cell cycle gene, and an antisense nucleic acid complementary to a nucleic acid encoding an oncogene.

74. The cell of claim 73, wherein said isolated nucleic acid is operably linked to a promoter/regulatory sequence.

75. The cell of claim 74, wherein said promoter/regulatory sequence is selected from the group consisting of a retroviral long terminal repeat, and the cytomegalovirus immediate early promoter.

76. An isolated purified population of long-term repopulating human hematopoietic stem cells obtained by a method comprising obtaining a population of cells from human hematopoietic tissue, isolating a population of KDR^+ hematopoietic stem cells therefrom, and incubating said population of KDR^+ cells with vascular endothelial growth factor, thereby expanding said population of long-term repopulating human hematopoietic stem cells.

77. A cell obtained using a method comprising obtaining a population of cells from human hematopoietic tissue, isolating a population of KDR^+ hematopoietic stem cells therefrom, and incubating said population of KDR^+ cells with vascular endothelial growth factor, thereby expanding said population of long-term repopulating human hematopoietic stem cells.

78. The cell of claim 77, wherein said cell comprises an isolated nucleic acid.

79. The cell of claim 78, wherein said isolated nucleic acid is selected from the group consisting of a nucleic acid encoding adenosine deaminase, a nucleic acid encoding beta-globin, a nucleic acid encoding multiple drug resistance, an antisense nucleic acid complementary to a human immunodeficiency virus nucleic acid, an antisense nucleic acid complementary to a nucleic acid encoding a cell cycle gene, and an antisense nucleic acid complementary to a nucleic acid encoding an oncogene.

80. The cell of claim 79, wherein said isolated nucleic acid is operably linked to a promoter/regulatory sequence.

81. The cell of claim 80, wherein said promoter/regulatory sequence is selected from the group consisting of a retroviral long terminal repeat, and the cytomegalovirus immediate early promoter.

82. A blood substitute comprising the progeny cells of an isolated purified population of long term repopulating human hematopoietic stem cells.

83. The blood substitute of claim 82, wherein said progeny cells are selected from the group consisting of red blood cells, neutrophilic granulocytes, eosinophilic granulocytes, basophilic granulocytes, monocytes, dendritic cells, platelets, B lymphocytes, T lymphocytes, natural killer cells, and differentiated precursors thereof, and undifferentiated progenitors thereof.

84. A chimeric non-human mammal comprising at least one of an isolated and purified long-term repopulating human hematopoietic stem cell.

85. The chimeric mammal of claim 84, wherein said cell is introduced into said mammal using a method selected from the group consisting of transplantation, and blastocyst injection.

86. The non-human mammal of claim 85, wherein said mammal is selected from the group consisting of a mouse, a rat, a dog, a donkey, a sheep, a pig, a horse, a cow, a non-human primate.

87. A method of inhibiting rejection of a transplanted organ, said method comprising ablating the bone marrow of a transplant recipient and administering to said recipient a multi-lineage engrafting dose of an isolated and purified long-term repopulating human hematopoietic stem cell obtained from the hematopoietic tissue of the donor of said organ, thereby inhibiting rejection of a transplanted organ.

88. A method of transplanting an autologous human hematopoietic stem cell in a human, said method comprising obtaining a population of cells from the hematopoietic tissue of a human and isolating a population of non-malignant hematopoietic stem cells therefrom, ablating the bone marrow of said human, and administering at least one said isolated non-malignant hematopoietic stem cell to said human, thereby transplanting an autologous human hematopoietic stem cell in a human.

89. A method of monitoring the presence of KDR^+ stem cells in a human hematopoietic tissue in a human receiving therapy, said method comprising obtaining a sample of hematopoietic tissue from said human before, during and after said therapy, and measuring the number of KDR^+ stem cells in said sample, thereby monitoring the presence of KDR^+ stem cells in a human hematopoietic tissue obtained from a human receiving therapy.